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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,299	BARSOUM ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,34,35,38,39,41,42,44,46,52 and 55-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 34, 35, 38, 39, 41, 42, 44, 46, 52, and 55-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/29/07 has been entered.

Claims 1, 34, 52, 58, and 66 are amended.

Claim 53 is cancelled.

Claims 1, 34, 35, 38, 39, 41, 42, 44, 46, 52, and 55-66 are presently pending and considered.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of claims 53, all objections and/or rejections of such claims are rendered moot, and thus are withdrawn.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-66 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 58-66 encompass generic compositions comprising a generic viral vector encoding a therapeutic protein operably linked to a promoter functional in hepatocytes, and a generic liposome-encapsulated cytotoxin.

The only support for such compositions and methods found in the specification relating to such genera is the single species of liposome-encapsulated doxorubicin (e.g., pp. 14-15, paragraph bridging).

Still further, while the Art of record demonstrates a knowledge that liposome-encapsulated cytotoxic drugs will target and kill kupffer cells when administered through specific routes (e.g., Official Action of 9/18/06, p. 13), and hence, within the knowledge disclosed by the Examiner in the prosecution, such would be a method to specifically target and kill kupffer cells, however, obviousness does not supplant the need to demonstrate, either through explicit or implicit disclosure, that Applicant possessed the genera presently claimed.

Given that the only disclosure, both explicit (specification, pp. 14-15, paragraph bridging), and implicit (EXAMPLES), is that liposome-encapsulated doxorubicin may be used, the Artisan could not reasonably determine that Applicant possessed the genera presently claimed at the time of invention.

Hence, these claims are properly rejected for comprising new matter.

Response to Argument – new matter, liposomal cytotoxins

Applicant's argument of 8/29/07 has been fully considered but is not found persuasive.

Applicant argues, citing case law (i.e., Amgen v. Hoechst), that they are not required to provide a sufficient number of species of a well known genus (pp. 9-11).

Such is not persuasive. Amgen v. Hoechst is concerned with written description, and not a new matter rejection. In a new matter rejection, the amended claims must be supported by the specification, to evidence possession of the newly claimed limitation (e.g., In re Ruschig, Aumuller, Korger, Wagner, Scholz, and Bander, 154 USPQ 118; 123 (U.S. Court of Customs and Patent Appeals 1967). Arguing written description does not apply here, as the limitation requires an obviousness-type demonstration of possession, which clearly does not provide for possession. Possession would be provided by specific disclosure of such genera as being part of the invention.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 34, 35, 38, 39, 41, 42, 44, 46, 52, and 55-66 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims encompass a generic promoter functional in hepatocytes.

The Examiner has found no support for such limitation, either explicit or implicit, in the originally-filed specification and claims. Moreover, Applicant's support is limited to a single paragraph, reciting tissue specific promoters (Applicant's argument of 3/20/07, p. 9, paragraph 3, citing the specification, pp. 9-10, paragraph bridging). However, such does not provide sufficient support for promoters functional in a hepatocyte, as such would necessarily an obvious species within the genera of tissue specific promoters.

Moreover, nothing in the Art of record indicates that such promoters would be the promoter of choice, and hence, the Art does not contribute anything over the disclosure in the specification and claims as filed.

Hence, these claims are properly rejected for comprising new matter.

Response to Argument – New Matter, promoters

Applicant's argument of 8/29/07 has been fully considered but is not found persuasive.

Applicant argues that the promoters are not required to be tissue-specific, but instead only functional in hepatocytes (p. 11, paragraph 3).

Such is not persuasive, but instead, exacerbates the issue. The recitation in the specification of tissue-specific promoters supports tissue specific promoters, and would provide an obviousness type written description for those that are tissue specific for liver, however, the claim terminology is broader still, simply requiring the promoter to function in the liver, and not even be tissue specific for liver. Hence, the obviousness of it is even a larger stretch and implies a lack of possession at the time of invention.

Applicant argues that the claims are enabled for expression control elements in hepatocytes, and that current law does not require description or recitation of specific promoter sequences to demonstrate possession (pp. 11-13).

Such is not persuasive. Applicant must demonstrate possession of each claimed limitation. Applicant has not so-done, for similar reasoning as described with respect to the liposomally encapsulated cytotoxins, above. It is recommended that Applicant simply remove the limitation of the promoter functional in hepatocytes and simply require that the gene in the vector is expressed in the hepatocyte, subsequent to transformation of the hepatocyte. As such, the specific claiming of new matter is precluded, and the claims still fit the same genera as Applicant is claiming.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of the amendments to the claims, the rejections of Claims 1, 34-39, 41-44, 46, 52, and 54 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing hepatocyte expression of a therapeutic gene product, wherein the second viral vector or the liposome encapsulated cytotoxin reaches the liver prior to or at the same time as the first viral vector and expression is increased in the liver over that of administrations without the agent, does not reasonably provide enablement for increasing gene product levels in any tissue other than liver, or for viral vectors chemically conjugated to the agent, are withdrawn.

To wit, the method claims are now limited to require increased expression in the liver.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-66 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administrations of the liposomally-encapsulated cytotoxin which are not concurrent with that of administration of the viral vector, does not reasonably provide enablement for concurrent administrations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Due to the prosecution history discussing the subject rejection thoroughly, the rejection will be written in succinct form.

Applicant's claims encompass concurrent administration of the liposomally-encapsulated cytotoxin. The specification discusses and broadly discloses concurrent administrations, and Example 5 further demonstrates a specific embodiment of 24 hours prior to administration of the vector.

However, such is not enough for the Artisan to reasonably predict concurrent administrations would produce an efficacious effect: that of depleting the Kupffer cells and thereby reducing filtration of the vector and allowing increased transformation of the hepatocytes. To wit, it has long been known that Kupffer cell depletion by liposomally-

encapsulated cytotoxins allows increased transformation of hepatocytes in vivo, if administered 2 days before vector administration, due to depletion of Kupffer cells (i.e., killing of Kupffer cells) (e.g., Wolff, et al. (1997) Journal of Virology, 71(1): 624-29, ABSTRACT).

From this, the Artisan would not conclude that the Kupffer cells are killed immediately, as the cytotoxins, such as doxorubicin, inhibit production of new proteins but do not destroy the cell outright, and as such, time would be required to kill these cells. Therefore, the Artisan would not reasonably predict that any killing of these cells would occur sufficient to have increased transformation of hepatocytes if performed simultaneously.

Hence, it would be undue experimentation to find out of such was the case, and for which liposomally-encapsulated cytotoxins. Such is undue because it amounts to inventing specifically claimed embodiments.

Still further, because the composition of liposomal cytotoxin and vector and carrier is only taught for use in such a method of concurrent administration, it is similarly not enabled.

Therefore the claims not enabled for their fully claimed scope.

Claim Rejections - 35 USC § 102, Wilson

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 52 and 55 remain rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 6,001,557 to Wilson et al., for reasons of record.

The rejection is restated for clarity.

Wilson teaches production of adenoviruses by co-transfection of a shuttle vector containing the therapeutic minigene and missing essential genes, and a helper virus, carrying the genes required for production of virus, which may or may not be designed to be packaged efficiently (col. 5, paragraph 6). With regard to promoters active in the liver, the CMV promoter is taught, and such is functional in the liver (e.g., col. 8, paragraph 1). Moreover, by being in water, such claims encompass the pharmaceutically-acceptable carrier.

Further, the production of viral particles, when using the helper virus that is capable of being packaged, will necessarily produce the viral particles of helper virus and vector containing the therapeutic minigene.

Hence, the claims are anticipated.

Response to Argument, anticipation, Wilson

Applicant's argument of 8/29/07 has been fully considered but is not found persuasive.

Applicant argues that Wilson does not teach the viral particles, and the vectors are not co-administered (pp. 15-16).

Such is not persuasive. As has been stated, and is restated above, the particles are made after infection of the cells with both viruses, when the helper virus is capable of being packaged.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of the argument and amendments, the rejections of Claims 1, 38, 43, 52, and 54 under 35 U.S.C. 102(b) as being anticipated by US Pat No. 6,730,507 to Graham, et al., are withdrawn.

To wit, the claims require each vector to be administered within a 24 hour period, while the Artisan would understand Graham to encompass time frames much larger, as such is the time required to obtain an immune response to the first vector.

In light of the recent supreme court decision, KSR v. Teleflex, the following new rejections are also applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,025,195 to Sandig, et al., and Wolff, et al. (1997) Journal of Virology, 71(1): 624-29.

Sandig teaches AdV vectors comprising liver therapeutic transgenes, for liver-specific gene therapy (ABSTRACT). Such vectors may be administered, *inter alia*, systemically (EXAMPLE 1), and as they teach patients (col. 3, paragraph 6) and promoters active in man (col.

4, paragraph 7), it is also clear that the vectors are for treating humans, and must have promoters active in hepatocytes. Moreover, the vectors may be replication deficient (cols. 1-2, paragraph bridging). However, Sandig does not administration of an agent to decrease the uptake of the vector by Kupffer cells.

Wolff, as well as the art in general, already recognized that many liposomally-encompasulated suicide compounds, such as chloronidate, may be administered 2 days before vector administration, in order to deplete Kupffer cells and thereby decrease uptake of subsequently-delivered adenoviral vectors (e.g., ABSTRACT).

However, the Art did not specifically teach administrations of the liposomal cytotoxin less than 24 hours prior to vector administration.

On the other hand, the Artisan, upon reading the Wolff reference, would also have recognized that the simple administration of the viral vector at any time while the Kupffer cells were depleted would yield similar results. Hence, it would have been obvious to administer the vector at any time after depeleting the Kupffer cells, thereby allowing the Artisan to reduce the time frame between administrations to less than one hour post-liposomal cytoxin administration, and allow administrations to be carried out more expediently. The Artisan would have good reason to pursue the known options within his or her technical grasp. In turn, because the method simply requires the properties already known in the prior art, it would have been obvious to make the method.

However, for those embodiments requiring concurrent administration, the Artisan would not reasonably expect such to work, for reasons given in the enablement rejection, above.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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